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(FILE 'HOME' ENTERED AT 13:56:28 ON 26 AUG 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 13:56:41 ON 26 AUG 2003

L1 1 S PHOSPHOLABAN
L2 9 S PHOPHOLAMBAN
L3 8 DUP REM L2 (1 DUPLICATE REMOVED)

=> d bib ab 1-8 l3

L3 ANSWER 1 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2003:197102 BIOSIS
DN PREV200300197102
TI Compounds for deactivating phospholamban function on Ca-ATPase (**phopholamban** inhibitors.
AU Pollesello, Piero (1); Ovaska, Martti; Tenhunen, Jukka; Vidgren, Jukka; Yliperttula-Ikonen, Marjo; Tilgmann, Carola; Lotta, Timo; Kaivola, Juha
CS (1) Grankulla, Finland Finland
ASSIGNEE: Orion Corporation, Espoo, Finland
PI US 6538022 March 25, 2003
SO Official Gazette of the United States Patent and Trademark Office Patents, (Mar. 25 2003) Vol. 1268, No. 4, pp. No Pagination.
http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133.
DT Patent
LA English
AB This invention relates to determining the three-dimensional structure of the cytosolic domain of phospholamban (PLB) and its active site from NMR data of sufficiently high resolution for the three-dimensional structure determination. The invention also relates to methods for rational drug design enabling the design of phospholamban inhibitors based on using the three-dimensional structure data provided on computer readable media, as analyzed on a computer system having suitable computer algorithms. The invention also relates to phospholamban inhibiting compounds with certain structural, phsicochemical and spatial characteristics that allow for the interaction of said compounds with specific residues of phospholamban.

L3 ANSWER 2 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:61785 BIOSIS
DN PREV200100061785
TI Regulation of sarcoplasmic reticulum Ca2+ pumps.
AU MacLennan, D. H. (1)
CS (1) Banting and Best Department of Medical Research, University of Toronto, Toronto, Ontario, M5G1L6 Canada
SO Biochemical Society Transactions, (October, 2000) Vol. 28, No. 5, pp. A136. print.
Meeting Info.: 18th International Congress of Biochemistry and Molecular Biology Birmingham, UK July 16-20, 2000
ISSN: 0300-5127.
DT Conference
LA English
SL English

L3 ANSWER 3 OF 8 MEDLINE on STN
AN 95298769 MEDLINE
DN 95298769 PubMed ID: 7779806
TI Solution structure of the cytoplasmic domain of **phopholamban**: phosphorylation leads to a local perturbation in secondary structure.
AU Mortishire-Smith R J; Pitzenberger S M; Burke C J; Middaugh C R; Garsky V M; Johnson R G
CS Neuroscience Research Centre, Merck Sharp and Dohme Research Laboratories,

Harlow, Essex, United Kingdom.
SO BIOCHEMISTRY, (1995 Jun 13) 34 (23) 7603-13.
Journal code: 0370623. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199507
ED Entered STN: 19950726
Last Updated on STN: 19950726
Entered Medline: 19950719
AB Peptides representing the N-terminal domain (Ia) of the cardiac sarcoplasmic reticulum protein phospholamban (residues 1-25 [PLB(1-25)] and a phosphorylated form [pPLB(1-25)]) were synthesized and their conformations examined using circular dichroism and nuclear magnetic resonance spectroscopy. In aqueous solution, both PLB(1-25) and pPLB(1-25) adopt a primarily disordered conformation. In 30% trifluoroethanol/10 mM phosphate, PLB(1-25) exhibits a CD spectrum consistent with 60% helical structure. This value decreases to 27% for the phosphorylated peptide. CD spectra in 2% SDS indicate 40% alpha-helix for PLB(1-25) and 20% for pPLB(1-25). Full chemical shift assignments were obtained by conventional homonuclear NMR methodologies for both PLB(1-25) and pPLB(1-25) in 30% trifluoroethanol/water and 300 mM SDS. The solution structure of PLB(1-25) in 30% TFE/water was determined from distance geometry calculations using 54 NOE distance constraints and 17 torsion angle constraints. In the family of 20 calculated conformers, the root mean square deviation from the mean structure is 0.79 A for backbone heavy atoms of residues 1-17. The structure comprises a regular alpha-helix extending from M1 to S16 with the remaining C-terminal residues disordered. The calculated structure is supported by analysis of C alpha H secondary shifts which are significantly negative for residues 1-16. Chemical shift degeneracy is substantially more extensive in the phospho form and precludes a direct comparison of calculated structures. However, the magnitudes of upfield secondary shifts are decreased by 20% in residues 1-11 and are not significantly helical for residues 12-16 according to the criteria of Wishart et al. [(1992) Biochemistry 31, 1647-1651]. 3JHN alpha coupling constants measured for I12, R13, A15, and S16 also suggest that residues 12-16 undergo a local unwinding of the helix upon phosphorylation. Similar results are obtained for PLB(1-25) and pPLB(1-25) in 300 mM perdeuterated sodium dodecyl sulfate except that differences in backbone dynamics for the helical and nonhelical regions of the peptide are evident in the DQF-COSY line shapes for fingerprint cross-peaks. This disruption of structure at the C-terminus of the helix suggests a model for phosphorylation-induced dissociation of the PLB/Ca(2+)-ATPase complex.

L3 ANSWER 4 OF 8 MEDLINE on STN DUPLICATE 1
AN 92299178 MEDLINE
DN 92299178 PubMed ID: 1535055
TI Gene expression of GLUT4 in skeletal muscle from insulin-resistant patients with obesity, IGT, GDM, and NIDDM.
AU Garvey W T; Maianu L; Hancock J A; Golichowski A M; Baron A
CS Section of Endocrinology, Indianapolis Veterans Administration Medical Center, IN.
NC DK-38765 (NIDDK)
DK-42469 (NIDDK)
SO DIABETES, (1992 Apr) 41 (4) 465-75.
Journal code: 0372763. ISSN: 0012-1797.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199207
ED Entered STN: 19920731

Last Updated on STN: 19920731
Entered Medline: 19920723

AB In obesity, impaired glucose tolerance (IGT), non-insulin-dependent diabetes mellitus (NIDDM), and gestational diabetes mellitus (GDM), defects in glucose transport system activity, contribute to insulin resistance in target tissues. In adipocytes from obese and NIDDM patients, we found that pretranslational suppression of the insulin-responsive GLUT4 glucose transporter isoform is a major cause of cellular insulin resistance; however, whether this process is operative in skeletal muscle is not clear. To address this issue, we performed percutaneous biopsies of the vastus lateralis in lean and obese control subjects and in obese patients with IGT and NIDDM and open biopsies of the rectus abdominis at cesarian section in lean and obese gravidas and gravidas with GDM. GLUT4 was measured in total postnuclear membrane fractions from both muscles by immunoblot analyses. The maximally insulin-stimulated rate of in vivo glucose disposal, assessed with euglycemic glucose clamps, decreased 26% in obesity and 74% in NIDDM, reflecting diminished glucose uptake by muscle. However, in vastus lateralis, relative amounts of GLUT4 per milligram membrane protein were similar (NS) among lean (1.0 +/- 0.2) and obese (1.5 +/- 0.3) subjects and patients with IGT (1.4 +/- 0.2) and NIDDM (1.2 +/- 0.2). GLUT4 content was also unchanged when levels were normalized per wet weight, per total protein, and per DNA as an index of cell number. Levels of GLUT4 mRNA were similarly not affected by obesity, IGT, or NIDDM whether normalized per RNA or for the amount of an unrelated constitutive mRNA species. Because muscle fibers (types I and II) exhibit different capacities for insulin-mediated glucose uptake, we tested whether a change in fiber composition could cause insulin resistance without altering overall levels of GLUT4. However, we found that quantities of fiber-specific isoenzymes (**phopholamban** and types I and II Ca(2+)-ATPase) were similar in all subject groups. In rectus abdominis, GLUT4 content was similar in the lean, obese, and GDM gravidas whether normalized per milligram membrane protein (relative levels were 1.0 +/- 0.2, 1.3 +/- 0.1, and 1.0 +/- 0.2, respectively) or per wet weight, total protein, and DNA. We conclude that in human disease states characterized by insulin resistance, i.e., obesity, IGT, NIDDM, and GDM, GLUT4 gene expression is normal in vastus lateralis or rectus abdominis. To the extent that these muscles are representative of total muscle mass, insulin resistance in skeletal muscle may involve impaired GLUT4 function or translocation and not transporter depletion as observed in adipose tissue.

L3 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1989:149942 CAPLUS
DN 110:149942
TI Involvement of electrostatic phenomena in phospholamban-induced stimulation of calcium uptake into cardiac sarcoplasmic reticulum
AU Chiesi, Michele; Schwaller, Roland
CS Pharm. Div., Ciba-Geigy Ltd., Basel, Switz.
SO FEBS Letters (1989), 244(1), 241-4
CODEN: FEBLAL; ISSN: 0014-5793
DT Journal
LA English

AB The activity of the Ca2+-pumping ATPase of cardiac sarcoplasmic reticulum (SR) is controlled by the phosphorylation of the intrinsic regulatory protein **phopholamban** (I), which affects both the apparent Km(Ca2+) and the Vmax of the transport process. The correlation between phosphorylation of I and the surface potential of the SR membrane was investigated. This latter influenced the local concn. of relevant ionic species near biol. membranes and thus modulated the activity of ion pumps and channels. The partitioning of the anionic probe, 8-anilino-1-naphthalenesulfonate, into the SR membrane was found to be dependent on the phosphorylation level of I. Changes in the surface membrane potential of .ltoreq.7 mV could be obtained by phosphorylation. The increase in the apparent affinity of the Ca2+ pump for Ca2+ induced by I phosphorylation

was clearly reduced at high ionic strength, i.e., under conditions known to reduce the surface membrane potential and all processes dependent on it. The results showed that electrostatic phenomena can account, in good part, for the modulation of the Ca2+ pump by I in cardiac SR.

L3 ANSWER 6 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1989:91217 BIOSIS
DN BA87:45353
TI POSTMORTEM CHANGES IN THE LEVEL OF CALCIUM PUMPING ATPASE IN RAT HEART SARCOPLASMIC RETICULUM.
AU IWASA Y; ONAYA T
CS THIRD DEP. INTERN. MED., UNIV. YAMANASHI MED. SCH., TAMAHO, YAMANASHI-KEN 409-38, JPN.
SO FORENSIC SCI INT, (1988) 39 (1), 13-22.
CODEN: FSINDR. ISSN: 0379-0738.
FS BA; OLD
LA English
AB The activity of calcium pumping adenosine triphosphatase (Ca2+-ATPase) in cardiac sarcoplasmic reticulum plays a pivotal role in myocardiac contraction-relaxation. The Ca2+-ATPase activity is controlled by phosphorylation and dephosphorylation of a sarcoplasmic reticulum protein "phospholamban" in response to neurotransmitters and drugs. To clarify the role of Ca2+-ATPase in the development of cardiac rigor morits, we examined the changes of cardiac rigidity and cardiac sarcoplasmic reticulum Ca2-ATPase activity up to 5 h after the decapitation of rats. Fifteen minutes after decapitation, the rats showed a cardiac rigidity on left ventricles. After 30 min, rigidity was obvious over the whole heart. After 1 h, the rigidity reached a high degree which was maintained for the rest of the observation period. On the other hand, the Ca2+-ATPase activity controlled by phosphorylation and dephosphorylation of phospholamban did not change for the whole observation period (5 h). Another Ca2+-ATPase activity representing the total amount of Ca2+-ATPase in sarcoplasmic reticulum gradually decreased. The data suggest that no significant phosphorylation or dephosphorylation of **phopholamban** occurs for a short time, at least for 5 h, after death and that the Ca2+-ATPase tends to relax the myocardium against the development of cardiac rigor mortis.

L3 ANSWER 7 OF 8 MEDLINE on STN
AN 76153441 MEDLINE
DN 76153441 PubMed ID: 176697
TI Regulation of calcium transport in cardiac sarcoplasmic reticulum by cyclic AMP-dependent protein kinase.
AU Tada M; Kirchberger M A; Katz A M
SO RECENT ADVANCES IN STUDIES ON CARDIAC STRUCTURE AND METABOLISM, (1976) 9 225-39. Ref: 48
Journal code: 0325677. ISSN: 0363-5872.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 197606
ED Entered STN: 19900313
Last Updated on STN: 19970203
Entered Medline: 19760602
AB A manyfold increase in phosphorylation of cardiac sarcoplasmic reticulum (SR) was seen when SR was incubated in the presence of a bovine cardiac cyclic AMP-dependent protein kinase and cyclic AMP. This phosphoprotein had stability characteristics of a phosphoester in which the phosphate is incorporated largely into serine, and its formation did not required calcium ions, unlike the formation of acyl phosphoprotein intermediate of calcium-transport ATPase which is present within the same membrane. When examined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, the

protein kinase-catalyzed phosphorylation occurred at a 22,000-dalton component of the cardiac sarcoplasmic reticulum. This 22,000-dalton protein has been named "phospholamban" (lambda alpha mu beta alpha nu epsilon iota nu = to receive), based on its ability to receive phosphate from ATP. Phosphorylation of phospholamban by cyclic AMP-dependent protein kinase was associated with the stimulation of calcium transport by the cardiac sarcoplasmic reticulum. This stimulation was accompanied by an increase in the calcium-activated ATPase activity, indicating that the overall rate of calcium transport rather than its efficiency is enhanced by protein kinase. The 22,000-dalton **phopholamban** was susceptible to trypsin. Brief digestion with trypsin in the presence of 1 M sucrose prevented subsequent phosphorylation of phospholamban, while leaving the calcium pump apparently intact. Incubation of trypsin-treated sarcoplasmic reticulum with cyclic AMP-depentent protein kinase did not result in the stimulation of calcium transport. These results may suggest that phospholamban is a modulator of the calcium pump of the cardiac sarcoplasmic reticulum.

L3 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1975:602815 CAPLUS
DN 83:202815
TI Phospholamban. Regulatory protein of the cardiac sarcoplasmic reticulum
AU Kirchberger, M. A.; Tada, M.; Katz, A. M.
CS Mt. Sinai Sch. Med., City Univ. New York, New York, NY, USA
SO Recent Advances in Studies on Cardiac Structure and Metabolism (1975), 5, 103-15
CODEN: RCSMCP; ISSN: 0363-5872
DT Journal
LA English
AB Accelerated Ca transport into the sarcoplasmic reticulum (SR) of the heart may mediate the inotropic actions of agents that act to increase cyclic AMP within the cell. ATP-dependent Ca uptake by cardiac microsomes rich in SR was enhanced by pretreatment with bovine cardiac cyclic AMP-dependent protein kinase (cyclic AMP-PK). Ca2+-activated ATPase was increased concomitantly with Ca uptake, stoichiometric coupling of 2 moles of Ca2+ taken up per mole of ATP hydrolyzed remaining const. The steady state level of Ca binding was not increased by cyclic AMP-PK pretreatment, suggesting that the turnover rate of the transport system rather than the no. of transport sites is increased. Phosphorylation of the SR by protein kinase was half-maximal at .apprx.10-7M cyclic AMP, a value similar to that which gives half-maximal stimulation of both Ca uptake and Ca2+-activated ATPase. Over 80 percent of the 32P assocd. with membrane protein was identifiable as phosphoserine and phosphothreonine. The 32P was incorporated into a 22,000 dalton protein as detd. by Na dodecyl sulfate-polyacrylamide gel electrophoresis. This protein, tentatively named phospholamban, appears to participate in the regulation of Ca transport by the heart's SR and may play a role in the inotropic actions of drugs, such as epinephrine, which act upon the cyclic AMP-PK system.

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